L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:435076 CAPLUS Full-text
DN 135:46205
TI Preparation of neurotrophic bicyclic diamides with peptidylprolyl isomerase (PPIase or rotamase) inhibitory activity
IN Dubowchik, Gene Michael; Provencal, David Paul
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001042245	A1	20010614	WO 2000-US32395	20001128

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-169600P P 19991208
OS MARPAT 135:46205
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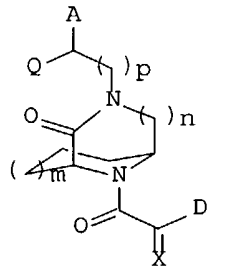

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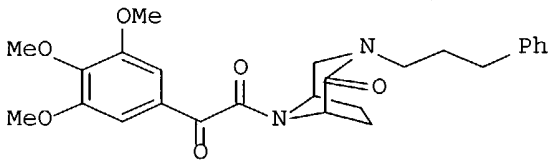


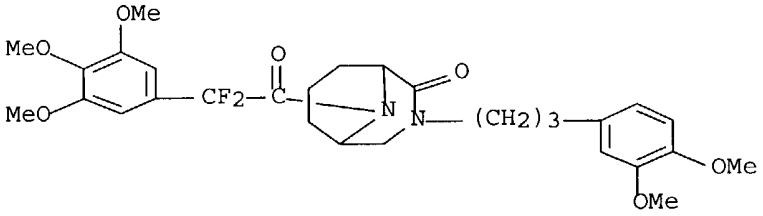
II

AB The invention relates to the design, synthesis, and the peptidylprolyl isomerase (PPIase or rotamase) inhibitory activity of novel bicyclic diamide compds. that are neuroprotective and/or neurotrophic agents (i.e. compds. capable of stimulating growth or proliferation of nervous tissue), and that bind to immunophilins such as FKBP12 and inhibit their rotamase activity. This invention also relates to pharmaceutical compns. comprising these compds. The compds. are encompassed by structure I [X = O, F2; n = 1, 2; m = 0, 1, 2; p = 0, 1; D = alk(en)yl, cycloalk(en), alk(en)yloxy, 2- or 3-indolyl, Ar, Ar-alk(en)yl; Ar = selected (un)substituted carbo- or heterocyclic aromatic groups; Q, A = H, Ar, alk(en/yn)yl, cycloalk(en)ylalk(en/yn)yl, their N/O/S-heteroat. analogs, etc.; and their pharmaceutically acceptable salts]. Over 40 examples were prepared and tested. For instance, (1S,5R)-8-benzyl-3,8-diaza-3-(3- phenylpropyl)bicyclo[3.2.1]octan-2-one (preparation given) underwent hydrogenolytic debenzylation and amidation with 3,4,5-trimethoxyphenyl-2- oxoacetyl chloride to give title compound II. In a fluorescence polarization assay of FKBP12 binding, II gave 34% inhibition at 1 μM, and its 3-(3-pyridyloxy)propyl analog gave 98% inhibition.

IT **344462-06-2P 344462-07-3P 344462-08-4P**
344462-09-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (stereoselective preparation and biol. activity of bicyclic diamides as neuroprotective agents and peptidylprolyl isomerase (PPIase or rotamase) inhibitors)

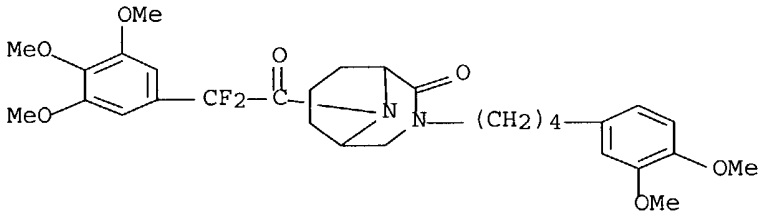
RN 344462-06-2 CAPLUS

CN 3,9-Diazabicyclo[3.3.1]nonan-2-one, 9-[difluoro(3,4,5-trimethoxyphenyl)acetyl]-3-[3-(3,4-dimethoxyphenyl)propyl]- (9CI) (CA INDEX NAME)



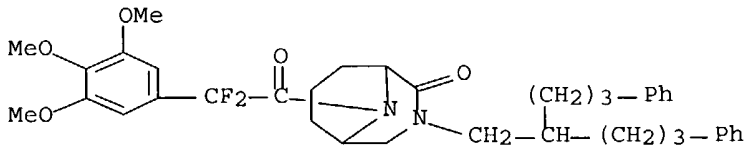
RN 344462-07-3 CAPLUS

CN 3,9-Diazabicyclo[3.3.1]nonan-2-one, 9-[difluoro(3,4,5-trimethoxyphenyl)acetyl]-3-[4-(3,4-dimethoxyphenyl)butyl]- (9CI) (CA INDEX NAME)



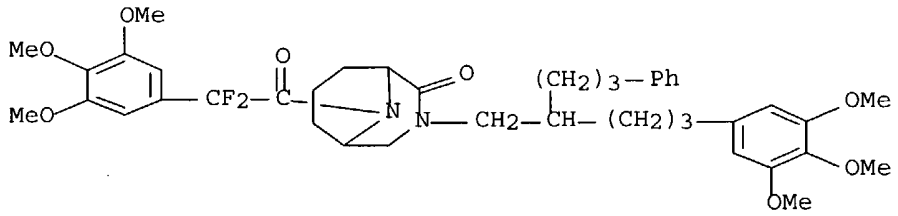
RN 344462-08-4 CAPLUS

CN 3,9-Diazabicyclo[3.3.1]nonan-2-one, 9-[difluoro(3,4,5-trimethoxyphenyl)acetyl]-3-[5-phenyl-2-(3-phenylpropyl)pentyl]- (9CI) (CA INDEX NAME)



RN 344462-09-5 CAPLUS

CN 3,9-Diazabicyclo[3.3.1]nonan-2-one, 9-[difluoro(3,4,5-trimethoxyphenyl)acetyl]-3-[2-(3-phenylpropyl)-5-(3,4,5-trimethoxyphenyl)pentyl]- (9CI) (CA INDEX NAME)



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

L7 ANSWER 1 OF 1 MARPAT COPYRIGHT 2004 ACS on STN
AN 137:370075 MARPAT Full-text
TI Preparation of diazabicyclo[3.3.1]nonane derivatives as FKBP-ligands
IN Guo, Chuangxing; Augelli-Szafran, Corinne E.; Barta, Nancy Sue; Bender, Steven Lee; Bigge, Christopher Franklin; Caprathe, Bradley William; Chatterjee, Arindam; Deal, Judith; Dong, Liming; Fay, Lorraine Kathleen; Hou, Xinjun; Hudack, Raymond Andrew, Jr.
PA Agouron Pharmaceuticals, Inc., USA; Warner-Lambert Company
SO PCT Int. Appl., 177 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002089806	A1	20021114	WO 2002-US14966	20020510
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1423119	A1	20040602	EP 2002-731761	20020510
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRAI US 2001-289828P 20010510
WO 2002-US14966 20020510
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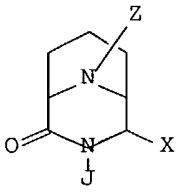

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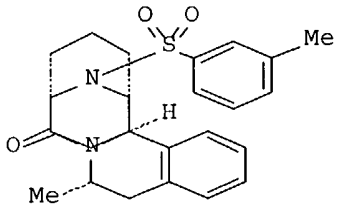


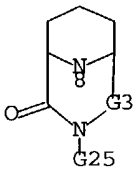
II

AB Title compds. I [Z = sulfonyl, acyl, etc.; J = H, alk(en)yl, cycloalkyl, aryl, heteroaryl; X = H, CN, alkoxy, dimethoxymethyl, oxygen (when the C-X bond is a double bond); X, J taken together with the N to form a (un)substituted heteroaryl, heterocycloalkyl] were prepared Over 130 example compds. were prepared and tested. For instance, 2,6-pyrdinedicarboxylic acid was reduced to the corresponding cis-piperidine dicarboxylic acid (H2O, NaOH, H2-Rh/Al, 55 psi, 48 h) and converted to the N-Cbz derivative This intermediate was converted to the bicyclic anhydride (Ac2O, 70°) and subsequently reacted with L-amphetamine to provide the corresponding imide (Ac2O, 110°). Reduction of the imide (THF/MeOH, NaBH4, -5°, 55 min), cyclization (CH2Cl2, TFA), removal of the Cbz group (EtOH/EtOAc, H2-Pd/C) and sulfonylation with m-toluenesulfonyl chloride provided II. Compds. of the invention inhibit FKBP-12 rotamase (peptidyl-prolyl isomerase) activity; II had Ki = 0.32 μM. I are useful for the treatment of peripheral neuropathies.

MSTR 1

G7—G1

G1 = 8



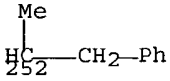
G3 = 75

HC(75)—G4

G7 = 198

C(198)(O)-CF_2—G8

G25 = 252



MPL: claim 1
NTE: also incorporates claim 15
NTE: or pharmaceutically acceptable salts, solvates, prodrugs, or pharmacologically active metabolites

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d l1; d his; log y
L1 HAS NO ANSWERS
L1                STR
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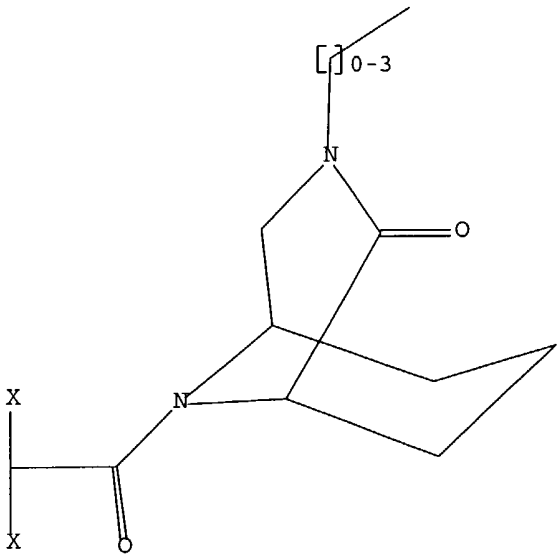

G1 O,X

Structure attributes must be viewed using STN Express query preparation.

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L3              4 S L1 FUL

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L4              1 S L3

     FILE 'BEILSTEIN' ENTERED AT 18:40:57 ON 02 JUN 2004
L5              0 S L1 FUL

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L6              2 S L1 FUL
L7              1 S L6 NOT L4

COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                              -0.66      -1.35

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